action mailed 09/10/04. These reasons may have been inadvertently overlooked in Applicants' last response or perhaps not handled to the Examiner's satisfaction. In either case, since the rejection of Claim 3 under paragraph 16 (i) is not clearly explained, Applicants are not certain of an appropriate response. Nevertheless, Claim 2 has been canceled and Claim 3 has been amended for the better readability thereof in a good faith attempt to overcome the remaining rejections under 35 U.S.C. § 112, second paragraph, and advance prosecution towards allowance. Amended Claim 3 omits "or the disease caused by the antigen" and, instead, lists the well-known viral antigens that correspond to certain clinical or medical conditions or diseases to which the Examiner had referred under paragraph (f) of the Office action mailed 09/10/04.

As a consequence of amending Claim 3, obvious typographical or clerical errors came to light in that the terms "Feline rhinotrachelitis" and "cauidiosis" should read "Feline rhinotracheitis" and "coccidiosis" (a major disease of poultry and swine), respectively. The present amendment corrects the spelling of Feline rhinotracheitis in Claim 3. The amendment also corrects the spelling of the disease coccidiosis, along with *Serpulina pilosicoli* and Turkey rhinotracheitis, in the specification on page 8, lines 24-26. However, it was realized that since a protozoan agent causes coccidiosis, the use of the term in Claim 3 would not find proper antecedent basis in the bacterial or viral antigen of Claim 1. For this reason, a new Claim 31 is presented that is drawn to the method of providing protection against the disease of coccidiosis. Support for the claim is found in original Claim 3 and the specification on page 8, lines 24-26.

Noted above, the Examiner has generously withdrawn many of the rejections of record. Out of the last twelve references cited against the claims under 35 U.S.C. § 103(a), six references remain in four different combinations for reasons given in paragraphs 22-25 on pages 5-12 of the Office action. In summary, the Examiner continues to apply the following groups:

(1) rejection of Claims 1-7, 9 and 28-30 as being unpatentable over Brinton *et al.* in view of Strobel *et al.* and Collins *et al.* (Paragraph 22);

(2) rejection of Claim 10 as being unpatentable over Brinton *et al.* as modified by Strobel *et al.* and Collins *et al.*, and further in view of Roland (Paragraph 23);

(3) rejection of Claim 27 as being unpatentable over Brinton *et al.* as modified by Strobel *et al.* and Collins *et al.*, and further in view of Mitani *et al.* (Paragraph 24); and

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(4) rejection of Claims 1-8 and 28-30 as being unpatentable over Bricker *et al.* in view of Strobel *et al.* and Collins *et al.* (Paragraph 25).

For the below reasons and remarks of record, Applicants respectfully traverse these rejections.

There have been long-standing needs in the veterinary field to permit the efficacious, mass vaccination of animals and to avoid rejection of oral vaccines that were recognized but not yet solved. Now solving the long-felt problem, the present method improves mass vaccination and the protection of animals against disease through the addition of a critical component, namely, the water-soluble flavorants, to oral vaccines. Applicants discovered that, surprisingly, the addition of flavorants significantly improved the likelihood of successful administration and intake of oral veterinary vaccines. Quite beneficially, the improved oral method of mass vaccination of animals reduces the costs of individual administration, stress and meat damage that often occur with traditional parenteral vaccination programs. Overcoming the art-recognized problems, the present invention achieves successful vaccination of animals by providing improved compliance of animals to self-administer sufficient amounts of oral vaccine compositions, eliminating rejection (spitting out) of the oral vaccine and inducing increased intake of the vaccine.

As the Examiner appreciates, obviousness does not require absolute predictability, only a reasonable expectation of success. In the present case, however, the working examples demonstrate that the oral vaccination program of the present invention provides superior results from the addition of the water-soluble, palatable flavorant in which the results are unexpected and significant, *i.e.*, the results are greater than those that would have been expected from the art to an unobvious extent and the results are of a significant, practical advantage. Based on the teachings in the art cited by the Examiner, one of ordinary skill in the art would not have expected the huge success in the mass vaccination of animals as a consequence of the flavorant. To further distinguish the claimed method from the art, the present invention includes the limitation that it is the critical presence of the flavorant that improves protection against disease by inducing the increased intake of the vaccine by the animal.

Turning to the rejection of Claims 1-7, 9 and 28-30 (paragraph 22) and examining what the collective art of Brinton *et al.* in view of Strobel *et al.* and Collins *et al.* teaches to one of ordinary skill in the art, it is clear that the collective art does not embrace the claimed method, taken as a whole.

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Brinton *et al.* illustrate methods for immunizing poultry in which vaccine compositions can be mass administered to the poultry through oral intake of water. The reference is not concerned with solving the art-recognized problem of animals' rejection of oral vaccines or explaining how to actively induce the birds to consume greater amounts of vaccine formulation to obtain sufficient immunization of the flock. They do not add any flavorant or any other agent to improve consumption of the vaccine.

Strobel *et al.* teach a stable liquid form of amoxicillin for oral administration in an animal's drinking water that is formed by reaction with hydrocylated polycarboxylic acid to render the antibiotic ingestive and palatable. Strobel *et al.* indicate that to enhance the palatability of the solution even further, one may add flavorings *and/or* artificial sweeteners, which means to the ordinary practitioner that the palatability may be enhanced by (1) adding artificial sweeteners (sugar instead of artificial sweetener is also taught), ***or*** (2) artificial sweeteners ***and*** flavorings. The reference describes a generic mixture in which the flavoring agent makes up 0.1 to 5.0 weight percent of the composition and the artificial sweetener comprises 0.1 to 10 weight percent of the composition. A specific composition in Example 2 consists of 50 g of Nutrasweet and 5 g of strawberry flavoring. Example 6 demonstrates that the addition of sweetener increases the effective dose per unit weight of the pig. The reference neither discloses nor implies a single example of a mixture that includes a flavoring agent in the absence of sweetener.

As expressly taught by Strobel *et al.*, flavoring agents alone are clearly not a viable option. In no uncertain terms, patentees teach that it is the artificial sweetener that enhances the palatability of the hydroxyacylated amoxicillin solution. There is no similar showing of flavorants or any inference that flavorant alone will enhance the palatability of the hydroxyacylated amoxicillin solution to pigs. Based on the reference's express teachings, one of ordinary skill in the art would predict only that an artificial sweetener (or sugar) will improve self-administration of antibiotics to an animal such as a pig, but clearly not a flavorant alone (*i.e.*, instant Claim 1), and most definitely not a flavorant used in mass vaccination of numerous animals (*i.e.*, instant Claim 7). In effect, the reference teaches away from the claimed method.

Collins *et al.* concern methods for diagnosis of the causative agent of Mystery Swine Disease (MSD) and antibodies to the viral agent useful in diagnosis and treatment of MSD. The

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patentees suggest that the causative agent of MSD can be mixed with excipients and buffering agents for oral administration; and that these combinations can be formed into a powder or suspended in an aqueous solution such that these powders or solutions can be added to animal feed or to the animals' drinking water. They broadly suggest that the powders or suspended combinations in the aqueous solutions can be suitably sweetened or flavored by various known agents to promote the uptake of the vaccine orally by the pig. The examples, however, only show how to obtain a filtered homogenate from a pig infected with MSD and mix that homogenate with Freund's incomplete adjuvant for experimental injection. The bare suggestion that the combination containing the MSD infectious agent can be given in an oral composition that is suitably sweetened or flavored without exemplification is not enabling prior art. It is truly an invitation to experiment further.

The complete idea of an oral vaccine and addition of a flavoring agent to the oral vaccine to enhance protection against a disease, even against MSD, has not been exemplified or taught by the art. In order to render the claimed method obvious, the reference must enable one of ordinary skill in the art to make and practice the claimed method (*Rockwell International Corp. v. United States*, 147 F.3d 1358, 47 U.S.P.Q.2d 1027, 1032 (Fed. Cir. 1998)). The full scope of the claimed method must be shown by the reference, without having to resort to undue experimentation (*Durel Corp. v. Osram Sylvania Inc.,* 256 F.3d 1298, 59 U.S.P.Q.2d 1238, 1244 (Fed. Cir. 2001)). Under the circumstances, it is seen that Collins *et al.* do not meet the requirements of enabling prior art.

Interestingly enough, the Paul *et al.* reference cited by the Examiner of record but not relied upon, includes the exact same boilerplate sentences as Collins *et al.* contain, and broadly suggests that combinations of the infectious agent (pathogenic porcine respiratory coronavirus in Paul *et al.* and the MSD viral agent in Collins *et al.*) mixed with excipients and buffering agents can be formed into a powder or suspended in an aqueous solution such that the vaccine powders or solutions can be added to animal feed or to the animals' drinking water and suitably sweetened or flavored. Like Collins *et al.*, Paul *et al.* also fail to teach how to make an efficacious oral vaccine product that improves protection of an animal against disease.

Moreover, the fact that the pharmaceutical field has included flavoring agents in the past to make certain oral vaccines such as the live poliomyelitis oral vaccine more palatable to

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children does not teach or imply that flavoring agents should routinely be added to all oral vaccines or any oral vaccines given to animals. The palatability factor does not guarantee by itself that an oral veterinary vaccine will be self-administered, be efficacious and induce the increased intake by animals. In fact, if it did, we would not still have had the art-recognized problem in 2001 of how to achieve successful mass administration of oral vaccines to animals. It would have been resolved in 1960 when Rea Cox Herald first introduced the oral polio vaccine with cherry fruit flavoring aid.

Most importantly to this rejection, taking all of the combined references together does not result in the claimed method. Even if the teachings of the references were combined, one of ordinary skill in the art would not arrive at the present invention. First of all, Brinton *et al.* deal with the problem of immunizing poultry while Collins *et al.* and Strobel *et al.* relate to the problem of immunizing or treating pigs. None of this art shows how one could achieve and improve mass vaccination of a variety of animals, which is described in detail on pages 12 and 13 of the instant application.

Secondly, Strobel *et al.* specifically exemplify and stress the importance of adding a sweetener in providing antibiotics to herds of pigs. In sharp contrast, Applicants have advantageously and surprisingly found that they can eliminate the artificial sweetener or sugar in the animal's diet and add flavoring agent alone to significantly improve vaccination results.

Thirdly, none of the cited art teaches improving oral vaccination programs of animals through the addition of a water-soluble flavorant in the absence of adding a sweetener. It is certain that there is no way the ordinary practitioner would have found the same solution as Applicants did when addressing himself/herself to the same problem (animal rejection of oral doses). With the knowledge of the teachings of Strobel *et al.* in mind, the only reason someone would try the flavoring agent alone is with inventive curiosity, which negates obviousness. The unexpected criticality and benefits of the flavorant additive to the oral vaccine formulation of the present invention is neither taught nor suggested by the collective art.

Considering the rejection of Claim 10 (Paragraph 23) in view of the above references and further in view of Roland, Applicants respectfully disagree with the Examiner's reading of the reference's experimental use of the syringe to administer Roland's vaccine to birds and the art-recognized procedure of oral gavage.

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Roland describes a recombinant *Salmonella* vaccine for the oral immunization of birds. The patented invention provides an attenuated mutant of *Salmonella* but does not concern itself with how to improve the compliance of poultry in consuming the oral vaccine. Furthermore, Roland does not show that using a syringe is a routine procedure that will provide an effective amount of an oral vaccine to an animal.

The oral gavage using a feeding cannula attached to a syringe, which is described in Roland's examples, refers to a well-known experimental method for force-feeding drugs to non-compliant animals. Here is a typical description of oral gavage from Johns Hopkins Animal Care and Use Training manual, found online at http://www.jhu.edu/animalcare/Mouse.HTM#admin:

> Oral gavage is performed using a ball ended feeding needle. Estimate the distance that the needle needs to be inserted into the mouse (*usually from the nose to the first rib*) and mark it on the needle. Restrain the mouse with the head and body extended as straight as possible to facilitate introduction of the gavage needle. Introduce the needle in the space between the left incisors and molars, and gently direct it caudally toward the right ramus of the mandible. The mouse usually swallows as the feeding tube approaches the pharynx, facilitating entry into the esophagus. If the animal struggles or appears to be in respiratory difficulty withdraw the tube and begin all over again. Once the desired position is attained, inject the material and withdraw the syringe. Monitor the animal after the procedure to ensure that there are no adverse effects.

It is clear that Roland does not teach or imply that his oral gavage using a syringe could be used to successfully induce increased intake of the oral vaccine by an animal. Roland did not appreciate or solve the art-recognized problem of oral vaccine rejection by the animal. Without the forced-feeding aspect of the administration of his vaccine, the bird would have rejected his unpleasant vaccine, spit it out and not get an adequate dosage.

Moreover, combining Roland with the teachings of Brinton *et al.* as modified by Strobel *et al.* and Collins *et al.* would lead the ordinary practitioner away from the claimed method towards the addition of sweeteners to improve protection against disease, and not flavorants. The

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collective art totally fails to teach the critical limitations in the method of Claim 10. First, there is no reasonable expectation of success in administering the oral vaccine to an animal by syringe. Secondly, there is no teaching of using the syringe to administer a flavored vaccine formulation to an animal in the absence of a sweetener. Thirdly, without the presence of the sweetener taught in the art, one would expect the animal to reject the oral vaccine, spit the dose out and not get sufficient blood levels of antigen for protection against disease. It is clear that the practitioner simply would not arrive at the claimed method in view of the art.

Similarly, the rejection of Claim 27 (Paragraph 24) as being unpatentable over Brinton *et al.* as modified by Strobel *et al.* and Collins *et al.*, and further in view of Mitani *et al.* is not adequately justified. The deficiencies of the collective art are not rectified with the addition of Mitani *et al.*, which merely teach how to obtain apple water that appeals to humans.

Certainly, the water-soluble palatable fruit flavorants of Claim 27 that include apple flavorant do not stand alone as the present invention. Rather, the invention is drawn to the unique combination of an apple flavorant in the claim-recited method of the mass administration of an oral vaccine to animals through drinking water in which the flavorant improves the extent of protection against disease.

Looking at the collective art from a veterinary perspective and combining Mitani *et al.* with the primary and secondary references, Strobel *et al.* still indicate to the ordinary practitioner that the apple flavoring would be an insufficient attractant by itself. As taught in the art, a sweetener must be included in the vaccine formulation in order to induce animals to drink the vaccine-containing water and to allow the animals to get a sufficient amount of antigen in their systems to protect against disease. In sharp distinction, Applicants demonstrated that the sweetener is not necessary. Quite surprisingly, the claim-recited method can be practiced with the water-soluble flavorant alone, in the absence of the sweetener, and provide consistently effective protection from disease in mass vaccination programs (see Example 2 on pages 30-32 of the specification for illustration of the excellent results obtained with the claimed method). Based on the art, one would have no reasonable expectation of success of the claimed method in which an apple flavorant is employed in the absence of the sweetener.

Insofar as the rejection of Claims 1-8 and 28-30 (Paragraph 25) as being unpatentable over Bricker *et al.* in view of Strobel *et al.* and Collins *et al.* is concerned, the amendment of

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Claim 1 makes clear that the presence of the flavorant, as specifically taught in the application, improves protection against disease by inducing increased intake of the vaccine by the animal. Support for this amendment is found in the specification on page 5, line 31 to page 6, line 3; page 9, lines 13-15; and Example 2 on pages 30-32.

The claimed method of the present invention sharply contrasts with the poor results and partial protection obtained by Bricker *et al.* when they attempted to vaccinate turkeys via drinking water with the live *Erysipelothrix* vaccine. Particularly in view of Strobel *et al.*, the ordinary practitioner would not simply add flavoring agents to the turkeys' drinking water and expect or predict improved results in the method of Bricker *et al.* The practitioner would have no reasonable expectation of success in the absence of a sweetener based on the combined references. It is plain to see that one would not arrive at the excellent results of the present invention in light of the collective art.

In view of the present amendment, the foregoing remarks and the remarks of record, Applicants respectfully request that the rejections of Claims 1-10 and 27-30 under 35 U.S.C. § 103(a) be withdrawn and the pending claims be held patentable.

The Examiner is encouraged to contact the undersigned attorney to discuss any outstanding issues.

Accordingly, this application is now in condition for an allowance. Favorable treatment is respectfully urged.

Respectfully submitted,

WYETH

Date: August 23, 2005

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APPENDIX

AMENDMENT TO THE SPECIFICATION

Please replace the paragraph on page 8, lines 24-26 with the following paragraph:

Poultry - *Salmonella typhimurium,* ~~*Sepultina*~~ *Serpulina pilosicoli,* Marek's disease virus, Infectious bursal disease, Infectious bronchitis, Newcastle disease virus, Reo virus, Turkey ~~rhinotracheltis~~ rhinotracheitis, ~~Couidiosis~~ coccidiosis.

AMENDMENT TO THE CLAIMS

Claim 1 (Currently amended): A method of providing protection against a disease in an animal comprising:

(a) admixing a water soluble palatable flavorant selected from the group consisting of fruit, fish and meat flavorants with a water soluble vehicle suitable for an orally administered vaccine to create a mixture;

(b) further admixing with the mixture of step (a), an antigen which is an active component selected from the group consisting of a bacterium and a virus to thereby produce an oral vaccine; and

(c) administering the vaccine of step (b) to said animal to provide protection against the disease;

wherein the presence of the flavorant improves protection against the disease by inducing increased intake of the vaccine by the animal.

Claim 2 (Canceled).

Claim 3 (Currently amended): The method of claim [[2]] 1, wherein the antigen ~~or the disease caused by the antigen~~ is selected from the group consisting of *Erysipelothrix rhusiopathiae*, *Actinobacillus pleuropneumoniae*, *Mycoplasma hyopneumoniae*, *E. coli K88*, *K99*, *F41* and *987P*, *Clostridium perfringens type c*, *Salmonella choleraesuis*, *Bordetella bronchiseptica*, *Leptospira bratislava*, *Leptospira canicola*, *Leptospira grippotyphosa*, *Leptospira hardjo*, *Leptospira pomona*, *Leptospira canicola*, Porcine Influenza virus, Circovirus, Porcine Reproductive and Respiratory Syndrome (PRRS) virus, Swine pox virus, Rotavirus, Porcine Respiratory Coronavirus, Parvo virus, Pseudorabies virus, transmissible gastroenteritis virus ~~agent~~, *Streptococcus equi*, *Clostridium tetani*, Equine Influenza Virus A1 and A2 strains, Equine Rhinopneumonids type 1, 1b and 4, Eastern Equine Encephalomyelitis virus, Western Equine Encephalomyelitis virus, Venezuelan Equine Encephalomyelitis virus, Equine Rotavirus, *E. coli O157:H7*, *Pasteurella multocida*, *Pasteurella haemolytica*, *Clostridium perfringens type D*, *Clostridium chauvoel*, *Clostridium novyl*, *Clostridium septicum*, *Clostridium haemolyticum*,

Clostridium sodellii, *Salmonella dublin*, *Salmonella typhimurium*, Bovine Rotavirus, Bovine coronavirus, Bovine rhinotracheitis virus, Bovine diarrhea virus, Parainfluenza-3 virus, Respiratory syncytial virus, *Serpulina pilosicoli*, Marek's disease virus, Infectious bursal disease virus, Infectious bronchitis virus, Newcastle disease virus, Reo virus, Turkey rhinotracheitis virus, ~~Couidiosis~~[[,]] Canine *Borrelia burgdorferi*, Canine *Ehrlichia canis*, Canine *Bordetella bronchiseptica*, Canine *Giardia lamblia*, Canine distemper virus, Canine Adenovirus, Canine Coronavirus, Canine Parainfluenza virus, Canine Parvovirus, Canine Rabies virus, Feline *Chlamydia psittaci*, Feline immunodeficiency virus, Feline infectious peritonitis virus, Feline leukemia virus, Feline rhinotracheitis virus ~~rhinotrachelitis~~, Feline Panleukopenia virus, and Feline rabies virus.

Claim 4 (Original): The method of claim 1, wherein the vaccine is administered through drinking water.

Claim 5 (Previously presented): The method of claim 1, wherein the animal is selected from the group consisting of swine, poultry, cattle, sheep, goats, horse, cat and dog.

Claim 6 (Previously presented): The method of claim 1, wherein the animal is selected from the group consisting of swine and poultry.

Claim 7 (Previously presented): The method of claim 6, wherein the administration of the oral vaccine is by mass administration through drinking water.

Claim 8 (Previously presented): The method of claim 7, wherein the animal is a pig and the antigen is *Erysipelothrix rhusiopathiae*.

Claim 9 (Previously presented): The method of claim 1, wherein the animal is selected from the group consisting of dog and cat.

Claim 10 (Previously presented): The method of claim 7, wherein the administration of the oral vaccine is into the mouth through a syringe.

Claims 11-26 (Canceled).

Claim 27 (Previously presented): The method of claim 7 wherein the water soluble palatable fruit flavorant is selected from the group consisting of cherry flavorant, grape flavorant, watermelon flavorant, and apple flavorant.

Claim 28 (Previously presented): The method of claim 7 wherein the water soluble palatable fruit flavorant is strawberry flavorant.

Claim 29 (Previously presented): The method of claim 1 wherein the water soluble palatable flavorant is a fruit flavorant.

Claim 30 (Previously presented): The method of claim 29 wherein the fruit flavorant is strawberry flavorant.

Please insert new Claim 31:

Claim 31 (New): A method of providing protection against coccidiosis in an animal comprising:

(a) admixing a water soluble palatable flavorant selected from the group consisting of fruit, fish and meat flavorants with a water soluble vehicle suitable for an orally administered vaccine to create a mixture;

(b) further admixing with the mixture of step (a), an antigen which is capable of stimulating an immune response to coccidiosis as an active component to produce an oral vaccine; and

(c) administering the vaccine of step (b) to said animal to provide protection against the disease;

wherein the presence of the flavorant improves protection against the disease by inducing increased intake of the vaccine by the animal.